REMARKS

Reexamination and reconsideration in light of the foregoing proposed amendments and the following remarks is respectfully requested.

Claims 1 and 54-61 and 63-75 are pending in this application. Claims 2-53 and 62 have been canceled without prejudice or disclaimer. It is proposed to amend claims 1, 58-61, 64, 66, 67, 70, 71 and 73 have been amended. The claims as amended do not raise an issue of new matter and would not involve any new consideration and search. The amendments are discussed below. It is requested that the amendments as proposed be entered.

Rejection Under 35 U.S.C. § 101

Claims 1 and 58 stand rejected under 35 U.S.C. § 101 "because the claimed invention is directed to non-statutory subject matter." According to the Examiner, "[t]o the degree that the method of claim 1 is directed to a completely *in silico* method where the obtaining and testing steps are computational in nature rather than laboratory chemistry ..., the claims are considered to be non-statutory as they merely manipulate data." Applicants respectfully disagree. The Claim 1 is not a "completely *in silico* method." The claimed method recites step (C) which requires testing the compound for its ability to either modulate binding of a natural ligand to the EGF receptor, ErbB3 or ErbB4, or to modulate signal transduction by binding to the EGF receptor, ErbB2, ErbB3 or ErbB4. In order to emphasize this step, it is proposed to amend claim 1 to add step (D) to select a compound tested in step (C) that has the abilities required in step (C). Also, to further emphasize the testing environment, it is proposed to amend step (C) of claim 1 to specify that the compound is tested *in vivo* or *in vitro*. Support for the amendments can be found at page 8, lines 3-9 of the specification. For the foregoing reasons it is respectfully

requested that the rejection of claims 1 and 58 under 35 U.S.C. § 101 be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1 and 54-75 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description and enablement requirements of the statute. Claim 62 has been canceled, thereby rendering the rejection as to this claim moot.

The Examiner has rejected the claims on the basis that new matter was added to the claims in our previous response. In particular, the Examiner finds that there is no basis in the specification for new claim 57 and the following phrases in claim 1: "modulates binding of a natural ligand" and "modulates signal transduction via the EGF receptor ErbB2, ErbB3 or ErbB4."

With regard to the phrase "modulates binding of a natural ligand," the phrase is supported at page 6, lines 33-35 of the specification when read in conjunction with the description at page 6, lines 30-32 and page 16, lines 8-10 of the specification. Specifically, these sections of the specification when read together provide for the stereochemical interaction between the compound and the receptor site which is adapted to prevent the binding of a natural ligand of the EGF molecule, i.e., the compound prevents binding of the natural ligand of the EGF molecule to increase or decrease the activity mediated of the EGF receptor molecule. Accordingly, the objected to phrase is supported by the specification of the application.

With respect to the phrase "modulates signal transduction via the EGF receptor ErbB2, ErbB3 or ErbB4," support for this phrase can be found at page 16, lines 8-10 when read in

conjunction with the passages at page 16, lines 16-18 and page 4, lines 34-35 of the specification. When these passages are read together, the specification describes that the EGF receptor activity is modulated by the compound and that once the compound has been identified as modulating the EGF receptor, the ability of the compound to antagonize signal transduction via the EGF-R can be assessed. The specification discloses at page 4 that the EGF family of receptors includes the EGF receptor, ErbB2, ErbB3 and ErbB4. Accordingly, the specification supports the phrase objected to by the Examiner.

With regard to new claim 57, support for this claim is provided at page 16, lines 16-19 of the specification. The claim is dependent on claim 1 and requires in step (C) (ii) the testing of the compound for its ability to modulate EGF receptor, ErbB2, ErbB3 or ErbB4 mediated cell proliferation. The invention is directed to the EGF receptor family which includes, but is not limited to, the EGF receptor, ErbB2, ErbB3 and ErbB4. See page 4, lines 34 and 35 of the specification. The specification discloses at page 16, lines 16-19, that "[o]nce [the] candidate compounds have been identified, their ability to antagonize signal transduction via the EGF-R can be assessed using a number of routine *in vitro* cellular assays such as inhibition of EGF-mediated cell proliferation." Accordingly, claim 57 is supported by the specification of the present application.

The Examiner has further rejected claims 1 and 54-61 and 63-75 under 35 U.S.C. § 112, first paragraph, as not satisfying the enablement requirement of the statute. In particular, the Examiner finds that the "specification does not disclose any compounds meeting the structural and functional limitations as required by the claims."

The test for enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation. *United States V. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989); *In re Stephens*, 529 F.2d 1343, 1345, 188 USPQ 659, 661 (CCPA 1976). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1573, 224 USPQ 409, 411 (Fed. Cir. 1984). It is the function of the specification, not the claims, to set forth the practical limits of operation of an invention. *In re Johnson*, 558 F.2d 1008, 1017, 194 USPQ 187, 195 (CCPA 1977).

Examples exemplifying specific compounds or molecules for claimed step(A)(i)-(iii) of claim 1 are not required to support enablement. The specification, as a whole, must be considered to determine if the invention as disclosed is enabled. The invention is directed to a method of identifying a compound that possesses stereochemical complementarity with the molecule as well as possessing the ability to modulate a molecule of the EGF receptor family. The Examiner has not presented any evidence to show that this concept is not known in the art and would require undue experimentation by a person skilled in the art to practice the claimed invention.

The Examiner made a finding that "the claims can be considered to be effectively no different from obtaining and testing all potential compounds as all assessed compounds will be obtained and tested." It is proposed to amend claim 1 so that step (B) recites: "selecting a compound assessed in step (A) which possesses stereochemical complementarity to the

molecule." Not all molecules assessed in step A will exhibit stereochemical complementarity to the receptor molecule. Step (B), as it is proposed to be amended, would require a selection from all compounds tested of those exhibiting stereochemical complementarity to the receptor. Those compounds selected in step (B) are then subjected to *in vitro* or *in vivo* testing.

The Examiner also made a finding that the claims do not recite any scoring function or cut-off value to discriminate high ranking compounds from low ranking compounds. It is not necessary to provide these cut-off values, particularly in view of the requirement of a selection being made. The concept of "selecting" relates to a choice being made with respect to the best or most suitable compounds in terms of stereochemical complementarity to the molecule of present interest.

The Examiner made a further finding that there is no guidance in the specification as how to select "one or more subsets of said amino acids related to the coordinates shown in Figure 6 by whole body translations and/or rotations". First, Applicants wish to clarify the meaning of "whole body translations and/or rotations". As the Examiner is aware, the coordinates listed in Figure 6 describe the three-dimensional structure of the EGFR ectodomain (amino acids 1 - 621) in a specific orientation. All computer graphics programs used to study the three-dimensional structures of compounds, e.g. proteins, permit the operator to view the three-dimensional structure from any viewpoint by rotating it (whole body rotations) or moving it across the computer screen (whole body translations). In some programs the operator simply clicks on the graphic on the computer screen and moves it about using the mouse. In more sophisticated programs there are separate interfaces on the computer screen for rotation, translation and zoom. Whole body rotation and translation can be applied to the whole molecule or to selected

(defined) subsets of amino acids, e.g. those involved in a potential binding pocket. Selected subsets can be considered as equivalent to 'zooming in' for a closer inspection of the details of the interaction between the selected region of the protein and the docked chemical compound. Thus, the phrase "whole body translations and/or rotations" would be readily understood by a person having ordinary skill in the art.

The Examiner states that the specification provides no guidance on which subsets of amino acids to choose. A person having ordinary skill in the art would have understood, however, that the "subsets of amino acids" in this phrase corresponds to a potential binding pocket or binding site on the receptor molecule. Please note our arguments set forth on pages 7 and 8 of our previous response, which makes it clear that processes for selecting binding sites would have been well known to those skilled in the art and that the specification provides adequate guidance on preferred binding sites at, for example, page 5.

The Examiner made a finding that the specification does not clearly specify what is required to be performed in assessing "stereochemical complementarity". In particular, the Examiner asserts that the specification does not provide a specific definition of "stereochemical complementarity". The Examiner acknowledges that page 5, lines 12 -15 defines stereochemical complementarity in the context of 'lock-and-key' visualisation, but finds the additional references to "matching intra-site coordinates lining the groove of the particular receptor site" and the optimal "fit" to be confusing. The terms "stereochemical complementarity", "matching intra-site surface coordinates" and "optimizing, geometrically or chemically, the fit" are all synonymous terms and are commonly used in the art. The phrase 'stereochemical complementarity' was already well known in the art before the priority date of the present application. For example, a

search of the PubMed database using the term "stereochemical complementarity" yielded 31 references. See the list of references attached to this response as Exhibit A. Some examples of these references are set out below:

1. Bransome, E.D. et al.; "Apparent stereochemical complementarity of estrogens and helical cavities between DNA base pairs: implications for the mechanism of action of steroids," *J. Theor. Biol.* 1985 Jan 7; **112**(1):97-108.

2. Hendry, L.B.; "Drug design with a new type of molecular modeling based on stereochemical complementarity to gene structure," *J. Clin. Pharmacol.* 1993 Dec; **33**(12):1173-87.

3. Hendry, L.B. et al.; "The stereochemical complementarity of DNA and reproductive steroid hormones correlates with biological activity," *J. Steroid Biochem.* 1986; **24**:843-852.

4. Hendry, L.B and Mahesh V.B.; "Stereochemical complementarity of progesterone, RU486 and cavities between base pairs in partially unwound double stranded DNA assessed by computer modelling and energy calculations, " *J. Steroid Biochem. Mol. Biol.* 1992; **41**:647-651.

We also note that the terms "stereochemical fit" and "shape complementarity" are recited in the claims in U.S. Patent Nos. 4,461,619 and 6,184,241. Copies of the patents are attached as Exhibits B and C, respectively. For example, claim 1 of U.S. Patent No. 4,461,619 defines a method for determining the biological activity of a molecule which includes comparing the stereochemical properties of the molecule with respect to cavities in a nucleic acid complex to determine a "complementary fit", with a fit indicating the biological activity. Further, claim 1 of

U.S. Patent No. 6,184,241 defines an aspartic protease/inhibitor complex wherein a portion of the complex has a "shape complementarity" with at least a portion of the substrate binding site of the aspartic protease. A person skilled in the art would have understood that the concepts of "stereochemical fit" and "shape complementarity" are synonymous with "stereochemical complementarity."

The Examiner asserts that the specification does not clearly imply what is required to be performed in assessing stereochemical complementarity. The Applicants submit that this is covered by reference to the docking programs as set forth on pages 13-14 of the specification. These programs take each chemical compound and calculate the strength of its interaction with the selected binding site on the EGFR by calculating the H-bonds, the geometric shape complementarity, the hydrophobic interactions, the Van der Waals forces and the salt bridges. All of these parameters contribute to the strength of the interaction. Each compound is placed in a large number of orientations and the calculated strengths of these parameters are recorded for each orientation. A person of ordinary skill in the art would clearly understand what is required to be performed in assessing stereochemical complementarity in light of the references provided in the specification.

The Examiner contends that the claims do not require finding a binding pocket, using a known binding pocket or using a docking program. Finding a suitable binding site is inherent in the claim language. The claims require assessing the complementarity between the compound and the receptor molecule. The original claim language referred to assessing the stereochemical complementarity between the compound and a "topographic region" of the molecule. It is Applicants' position that the "topographic region" referred to a potential binding site on the

receptor molecule. At the interview with the Examiner last year on June 24, 2003, the Examiner suggested simply removing the term "topographic region" on the ground that the phrase "assessing the stereochemical complementarity between the compound and molecule" was clearer. We adopted the Examiner's suggestion and amended the claim accordingly. The phrase "one or more subsets or amino acids related to the coordinates shown in Figure 6 by whole body translations and/or rotations" in claimed step (A)(ii) of claim 1 clearly encompasses the concept of identifying binding pockets. In particular, a person of ordinary skill in the art would have understood that the selection of subsets of amino acids is equivalent to selecting a binding pocket for modeling purposes. The specification at pages 4 and 5 provides adequate guidance for selecting suitable "topographic regions" or binding pockets. In particular, on page 6, lines 1-8 of the specification states that

> ...the interaction of the compound causes the L1 and S1 domains to move away from each other. In a further preferred embodiment the compound interacts with the hinge region between the S1 domain and the L2 domain causing an alteration in the positions of these domains relative to each other. In a further preferred embodiment the compound interacts with the β sheet of the L1 domain causing an alteration in the position if the L1 domain relative to the position of the S1 domain or L2 domain.

The patent application goes even further by specifying two sites on the lower β-sheet of the L1 and L2 domains as suitable targets for screening. See, for example, the specification at page 6, lines 9-14. As we pointed out in our last response, Applicants submit that a person skilled in the art working in the field of *in silico* screening would be able to identify candidate binding pockets in any given 3D structure. In the present case, however, the patent application actually identifies specific "topographic regions" which represent preferred "binding pockets" within the EGFR

structure. These binding pockets can be used in screening methods to identify potential ligands and are described as follows:

(i) The fragment which includes residues 1-475 of the receptor, comprises the L1, S1 and L2 domains of the ectodomain of the EGF receptor. At the center of the structure is a cavity, bounded by all three domains, of sufficient size to accommodate a ligand molecule (see the specification at page 5, lines 5-7).

(ii) The fragment, which includes residues 313-621 of the receptor, comprises the L2 and S2 domains, which are positioned such that they form a "corner" structure. It is envisaged that this corner structure provides a further binding site for ligands of EGF receptor family members (see the specification at page 5, lines 8-11).

Accordingly, the patent application not only identifies the binding pockets within the EGFR structure, but suggests preferred regions within these binding pockets to use in screening for ligands. Armed with the atomic coordinates of the EGF receptor provided in the patent application and the information regarding preferred regions within specified binding pockets, it would have been a matter of routine for a person skilled in the area of *in silico* screening to utilize any one of the well known docking programs to screen for potential ligands.

For all of the foregoing reasons, it is respectfully requested that the Examiner reconsider and withdraw the rejection of claim 1 and 54-61 and 63-74 under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1 and 54-75 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 62 has been canceled, thereby rendering the rejection moot. The Examiner made a finding that claim 1 is unclear with respect to the phrases "natural ligand" and "signal transduction via the EGF receptor, ErbB2, ErbB3 or ErbB4". Applicants respectfully traverse this rejection.

The objected to phrases would be clearly understood by a person skilled in the art. In particular, the term "natural ligand" is well known in the art. Attached as Exhibit D is a summary from the USPTO web site of granted U.S. patents wherein the term "natural ligand" occurs in the abstracts or claims. The term does not relate to the setting, i.e. *in vivo* or *in vitro*, but rather to the ligand which binds to a receptor and which exists in nature, i.e. it is not artificial. The term does not exclude synthesized organic compounds if those compounds in fact exist in nature and are ligands of the EGF receptor, ErbB2, ErbB3 or ErbB4. It is proposed to amend claim 1 to make it clear that signal transduction is modulated by binding to the EGF receptor, ErbB2, ErbB3 or ErbB4.

The Examiner contends that "it is not known what the increase, decrease or inhibition" is in comparison to or when this step occurs within the method of claim 1. In our view this comment lacks merit. Step (C) of claim 1 requires testing the compound for its ability to modulate signal transduction of the receptor. A person of ordinary skill in the art would readily appreciate that the modulation, i.e. increase, decrease, or inhibition, would be relative to a control in which the compound is not present. The language of the claim would have been

understood by a person having ordinary skill in the art to mean that the increase, decrease or inhibition would occur during step (C) of claim 1 (i.e. during the *in vitro* or *in vivo* testing).

The Examiner finds that the phrases "substantially as shown" and "form an equivalent 3-dimensional structure" are indefinite and unclear. In order to obviate the objection to the phrase "substantially as shown", it is proposed to delete the phrase "substantially" from the claims. As for the objection to the phrase "form an equivalent 3-dimensional structure," this phrase would have been understood by a person skilled in the art when used in the context in which this phrase is used in the specification. The context is as follows: "amino acids present in the amino acid sequence of ErbB2, ErbB3 or ErbB4, which form an equivalent three-dimensional structure to that of the receptor site defined by amino acids 1-621 of the EGF receptor ...." Such a person would have been well aware that members of the EGF receptor family (i.e. the EGF receptor, ErbB2, ErbB3 and ErbB4) share equivalent structural domains, such as the L1, L2, S1 and S2 domains. It would be clear then to a person having ordinary skill in the art that the phrase "form equivalent three-dimensional structure" in the claims refers to a set of amino acids in the ErbB2, ErbB3 and ErbB4 receptors that form the equivalent domains to those formed by amino acids 1-621 of the EGF receptor.

The Examiner contends that there is no antecedent basis in claim 1 for the phrase "the molecule". The first appearing "the molecule" in claim 1 has been amended to recite --a molecule--. It is believed that by this amendment, the rejection is overcome.

The Examiner objects to claims 62 and 67 on the ground that the step of modifying the compound is confusing. In order to obviate this rejection, claim 62 has been canceled and claim 67 has been amended to recite that, *inter alia*, the step of modifying the compound selected in

step (B) or step (D) enhances the modified compound to bind to a lower face containing the second β-sheet of the L1 and/or L2 domains when compared to the unmodified compound.

Finally, the Examiner has objected to claim 73 as being unclear because it is not clear whether the K_d or K_I is "a predicted, calculated or experimentally determined value." Claim 73 has been amended to clarify this portion of the claim and to specify that the K_d and K_I are experimentally determined.

Conclusion

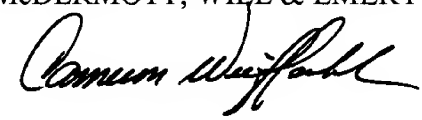
For the foregoing reasons, it is submitted that the claims 1, 54-61 and 63-75 are statutory subject matter under 35 U.S.C. § 101 and comply with the requirements of the first paragraph of 35 U.S.C. § 112. Accordingly, it is requested that the proposed amendments to the claim be entered and that favorable reconsideration of the claims is requested in light of the proposed amendments and remarks. Allowance of the claims is courteously solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including

extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT, WILL & EMERY



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